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MEMORANDUM

DATE: December 12, 2007

SUBJECT: **Thiencarbazone-Methyl:** Qualitative Risk Assessment Based On C57BL/6J Mouse Carcinogenicity Dietary Study

P.C. Code: 015804

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BACKGROUND

A carcinogenicity study in C57BL/6J mice was conducted by Bayer CropScience, Sophia Antipolis Cedex, France, for Bayer AG, Bayer CropScience, Monheim, Germany, and completed November 10, 2006 (Study No. SA 04062, MRID No. 47070135).

The study design allocated groups of 50 mice to dose levels of 0, 200, 1000 and 4000 ppm of Thiencarbazone-methyl for 78 weeks. Doses were equivalent to 0, 29.2, 147 and 599 mg/kg/day for males and 0, 36.8, 185 and 758 mg/kg/day for females. An additional ten mice per sex per dose were designated for interim sacrifice at week 29.

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ANALYSES

Survival Analyses

Male mice showed a statistically significant increasing trend for mortality with increasing doses of Thiencarbazone-methyl, as well as a significant pair-wise comparison of the 4000 ppm dose group with the controls, both at $p < 0.05$. There was not a statistically significant trend in mortality with increasing doses of Thiencarbazone-methyl in female mice, however, there was a statistically significant pair-wise comparison of the 200 ppm dose group with the controls at $p < 0.05$ (Tables 1 and 2).

Tumor Analyses

Male mice had statistically significant trends in bladder transitional cell papillomas and carcinomas, both at $p < 0.05$. There was also a statistically significant trend at $p < 0.01$, and a significant pair-wise comparison of the 4000 ppm dose group with the controls at $p < 0.05$, for bladder transitional cell papillomas and carcinomas combined. Female mice had a statistically significant trend in bladder transitional cell papillomas and carcinomas combined at $p < 0.05$, however, female mice had no significant pair-wise comparisons of the dosed groups with the controls. The statistical analyses of the tumors in the male mice were based upon Peto's Prevalence Test. The statistical analyses of the tumors in the female mice were based upon Fisher's Exact Test for pair-wise comparisons and the Exact Test for trend (Tables 3 and 4).

Table 1. Thiencarbazone-Methyl – C57BL/6J Mouse Study (MRID 47070135)

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks				
Dose (ppm)	1-28	29[i]	29-53	54-80[f]	Total
0	0/60	10/60	4/50	7/46	11/50 (22)*
200	4/60	9/56	1/47	12/46	17/51 (33)
1000	1/60	9/59	3/50	8/47	12/51 (24)
4000	1/60	10/59	6/49	15/43	22/50 (44)*

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifice at week 29.
[f]Final sacrifice at weeks 78-80.

( )Percent.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 2. Thiencarbazone-Methyl – C57BL/6J Mouse Study (MRID 47070135)

Female Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks				
Dose (ppm)	1-28	29[i]	29-53	54-80[f]	Total
0	0/60	10/60	3/50	3/47	6/50 (12)
200	2/60	10/58	2/48	10/46	14/50 (28)*
1000	1/60	10/59	1/49	2/48	4/50 (8)
4000	0/60	10/60	1/50	8/49	9/50 (18)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifice at week 29.
[f]Final sacrifice at weeks 78-80.

( )Percent.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 3. Thiencarbazone-Methyl – C57BL/6J Mouse Study (MRID 47070135)

Male Urinary Bladder and Urethra/Prostate Transitional Cell Tumor Rates[+] and Peto's Prevalence Test Results

	Dose (ppm)			
	0	200	1000	4000
Bladder Papillomas (%)	0/39 (0)	0/34 (0)	0/39 (0)	1[a]/28 (4)
p =	0.02686*	-	-	0.11896
Urethra Carcinomas (%)	0/38 (0)	0/34 (0)	0/37 (0)	1[b]/28 (4)
p =	0.02835*	-	-	0.12202
Combined (%)	0/38 (0)	0/34 (0)	0/37 (0)	2/28 (7)
p =	0.00342**	-	-	0.04842*

+Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before observation of the first tumor.

[a]First urinary bladder transitional cell papilloma observed at week 80, dose 4000 ppm, in a final sacrifice animal.
[b]First urethra/prostate transitional cell carcinoma observed at week 79, dose 4000 ppm, in a final sacrifice animal.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 4. Thiencarbazone-Methyl – C57BL/6J Mouse Study (MRID 47070135)

Female Bladder Transitional Cell Tumor Rates[+]
and Fisher's Exact Test and Exact Test for Trend Results

	Dose (ppm)			
	0	200	1000	4000
Papillomas (%)	0/45 (0)	0/45 (0)	0/46 (0)	2[a]/48 (4)
p =	0.06700	1.00000	1.00000	0.26367
Carcinomas (%)	0/45 (0)	0/45 (0)	0/46 (0)	1[b]/48 (2)
p =	0.2609	1.00000	1.00000	0.51613
Combined (%)	0/45 (0)	0/45 (0)	0/46 (0)	3/48 (6)
p =	0.01693*	1.00000	1.00000	0.13329

+Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 54.

[a]First papilloma observed at week 79, dose 4000 ppm, in a final sacrifice animal.
[b]First carcinoma observed at week 79, dose 4000 ppm, in a final sacrifice animal.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

References

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